

Response to: 'Does MOVES move the needle?' by Dr Meyer

We thank Dr Meyer¹ for his comments on the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)² and the Multicentre Osteoarthritis interVENTion trial with SYSADOA (MOVES).³

In GAIT, carried out during 2000–2004, 1583 patients with symptomatic knee osteoarthritis (OA) were randomised to glucosamine, chondroitin sulfate, glucosamine plus chondroitin sulfate, celecoxib or placebo. As Dr Meyer pointed out, there was a strong placebo response; after 24 weeks, 60.1% of the placebo group had a 20% decrease in Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score (primary outcome). However, Dr Meyer said that 'GAIT failed to show a difference for any treatment in the change from baseline'; the response rates in the four treatment groups were 64.0% for glucosamine ($p=0.30$), 65.4% for chondroitin sulfate ($p=0.17$), 66.6% for the combination ($p=0.09$) and 70.1% for celecoxib ($p=0.008$). Accordingly, celecoxib was significantly (ie, $p<0.017$ after adjustment for multiple comparisons) better than placebo.

GAIT² also examined treatment effects among patients with moderate-to-severe WOMAC pain. Among these subjects, response rates (20% decrease in WOMAC pain) were 54.3% (placebo), 65.7% (glucosamine; $p=0.17$), 61.4% (chondroitin sulfate; $p=0.39$), 79.2% (combination; $p=0.002$) and 69.4% (celecoxib; $p=0.06$). As Dr Meyer pointed out, the combination arm had a significantly better response than placebo, but contrary to his assertion that this was an 'exploratory analysis', it was a prespecified subgroup intended for analysis as patients were stratified at baseline according to their pain levels. The protocol stated that 'Logistical regression analysis will be used to determine whether the observed treatment effects in the primary analysis remain after adjustment for patient covariates such as...baseline measures of disease severity'. As logistical regression analysis showed a significant interaction between treatment and pain stratum, the results by pain stratum were analysed.²

In MOVES,³ carried out during 2011–2013, 606 patients with knee OA with moderate-to-severe WOMAC pain were randomised to glucosamine plus chondroitin sulfate or celecoxib. The primary outcome (mean decrease in WOMAC pain) was -185.7 in the glucosamine plus chondroitin sulfate group and -186.8 in the celecoxib group ($p=0.92$), showing non-inferiority.

Dr Meyer criticised the lack of a placebo group in MOVES, but this decision was taken for two reasons, the first because celecoxib has proven efficacy and the second because it was not considered appropriate to include a placebo arm for ethical and methodological reasons. Early randomised controlled trials (published in 1999–2001) showed celecoxib to be superior to placebo in patients with knee OA (eg, Bensen *et al*⁴). Since then, a number of non-inferiority studies have compared other COX-2 selective inhibitors to celecoxib and have not included.^{5 6} Methodologically, a non-inferiority trial requires that the

efficacy of the reference treatment is established or is in widespread use, so that a placebo or untreated control group would be deemed unethical.⁷ This is of special relevance in this specific population of patients with OA with moderate-to-severe pain. As celecoxib is approved by both the FDA and the EMA for the treatment of patients with OA, it was chosen as the reference treatment for the MOVES trial.

Overall, we feel that our choice of celecoxib as the sole, active, comparator was justified, and that the MOVES trial does show that glucosamine plus chondroitin sulfate is effective in patients with moderate-to-severe knee OA.

Marc C Hochberg, on behalf of the MOVES Investigation Group

University of Maryland School of Medicine, Baltimore, Maryland, USA

Correspondence to Marc C Hochberg, University of Maryland School of Medicine, 10 S. Pine St., MSTF 8-34, Baltimore, MD 21201, USA; mhochber@medicine.umaryland.edu

Competing interests MCH is a consultant to Bioiberica SA, Bristol Myers Squibb, Eli Lilly, EMD Serono SA, Iroko Pharmaceuticals, Novartis Pharma AG, Pfizer, Samumed LLC and Theralogix LLC and owns stock in Theralogix LLC.

Provenance and peer review Commissioned; internally peer reviewed.



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To cite Hochberg MC, on behalf of the MOVES Investigation Group. *Ann Rheum Dis* 2015;**74**:e36.

Received 6 March 2015

Accepted 7 March 2015



► <http://dx.doi.org/10.1136/annrheumdis-2015-207357>

Ann Rheum Dis 2015;**74**:e36. doi:10.1136/annrheumdis-2015-207426

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